

Durability of tetanus seroprotection in people living with HIV

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Objectives: The aim of this study was to estimate the durability of tetanus toxoid specific seroprotection in a cohort of people with HIV (PWH).

Design: A cross-sectional study.

Methods: PWH with a last date of tetanus toxoid booster available were identified. Tetanus toxoid specific IgG were detected using commercial ELISA kit. Durability of seroprotection was estimated using a linear regression model and analyzed according to the country of birth. The impact of baseline parameters at the time of vaccination (CD4^b T cell count, viral load, and antiretroviral therapy) was also assessed.

Results: One hundred three individuals were included. The median duration between last tetanus toxoid booster and sampling was 5.6years (IQR 2.6-8.9). Using a linear regression model, half-life of tetanus toxoid specific antibody was estimated at 9.9 years [95% confidence interval (95% CI: 5.5–50)] in the whole cohort. Half-life was reduced in individuals born outside Europe: 4.4 years (95% CI: 2.9– 8.5). PWH born outside Europe had lower CD4^b T cell count at the time of immunization and more frequently a CD4^b T cell count nadir less than 200 cells/ml before vaccination.

Conclusion: PWH born outside Europe have lower half-life of tetanus toxoid specific antibody as compared to previous study performed in the general population. Possible causes include lower nadir or current CD4^b T cell count or under-immunization status in country of origin before migration. Longer interval of booster vaccination, as recommended in the general population, might not be appropriate in this subgroup of PWH.

Keywords: antibodies, cross-sectional studies, HIV, immunological memory, tetanus, vaccine

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Introduction

Chronic HIV infection is associated with defective response to immunization. This includes lower seroconversion rate and lower durability of antibody response [1].

Tetanus, a lethal infection caused by the toxin of *Clostridium tetani*, is a vaccine preventable disease. Immunization against tetanus with tetanus toxoid is associated with long-lasting antibody response in the general population. WHO guidelines consider as protective a concentration of tetanus toxoid IgG more than 0.1 UI/ml [2]. Studies performed in the general population in different countries indicates that TT vaccine-induced protection can last up to 20–70 years [3–5]. On the basis of these findings, WHO recommends since 2017 no additional booster in individuals having completed primary childhood immunization series [6]. A recent study assessed tetanus incidence in countries providing adults a booster as compared to countries not vaccinating adults. Adult booster immunization had no impact on the incidence of tetanus in a large review of 11 billions person-years of incidence data [7].

Response to tetanus toxoid immunization in people with HIV (PWH) has only been assessed in a restricted number of studies with a limited number of individuals included. Moreover, the response was only assessed shortly after immunization [8,9]. Current guidelines for PWH regarding tetanus toxoid booster administration are thus based on assumption from the studies performed in the general population [10]. Whether specific booster administration strategies are required for PWH, or subgroups of PWH is currently unknown. In the present study, we assessed the durability of tetanus toxoid specific antibody response in a cohort of PWH with documented tetanus toxoid immunization using a linear regression model.

Materials and methods

Patient and data collection

From January 2018 to February 2019, we prospectively enrolled PWH attending the outpatient clinic of Centre Hospitalier Universitaire Saint-Pierre, one of the AIDS Reference Center in Belgium. Collected data included socio-demographics characteristics, HIV-infection related data and information about tetanus toxoid immunization. Study data were collected and managed using REDCap electronic data capture tools hosted at CHU Saint-Pierre [11]. Documented date of tetanus toxoid immunization was retrieved from medical files, immunization card, or direct contact with the general practitioner of the patient. The study was approved by the local ethic committee (BE076201734347) and all participants signed an informed consent.

TT-IgG ELISA

Tetanus toxoid specific IgG were detected using commercial ELISA kit (TheBindingSite, Birmingham, UK) in serum or plasma following manufacturer's instructions.

Statistical analyses

The duration of protection was analyzed by a linear regression model as previously described [3]. In this model, tetanus-specific antibody levels at more than 1 year after vaccination are the dependent variable and the time since vaccination is the independent variable in the following equation: $\log(\text{antibody titer}) = \frac{1}{4} a - b \times \text{years} + e$, where a represents mean log titer at time of vaccination; b , decay rate or average log titer change per year; and e , error term. The coefficient estimated by the model for the independent variable (b) gives the rate of decline per year and is used to estimate ATA half-life using the following formula: $\log(0.5)/b$. The complementary analyses by subgroup of subjects were performed using the same linear regression model in which the interaction between the groups is taken into account. A significant interaction between subgroups indicated a significant difference in the antibody decay rate.

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Carolina, USA) and R [12].

Results

Study population

During the study period, 344 PWH were recruited and had serum or plasma available for testing. Considering the distinct immune response following immunization observed in perinatally infected individuals, which is associated with shorter duration of vaccine-specific immune responses [1,13], the latter were excluded ($n = 11$). Vaccine documentation for a tetanus toxoid booster was found in 152 patients. Of those, 23 were vaccinated before HIV diagnosis and were excluded. Two individuals taking immunosuppressive drugs at the time of sampling were excluded. Finally, only the individuals with a delay between the vaccination date and sampling at least 1 year ($n = 103$) were retained for analysis in order to coincide with previous reference study in the general population [3].

Characteristics of the individuals at the time of vaccination and sampling are presented in Table 1 according to the region of origin (Europe vs. Non-Europe). The majority of non-European individuals were women and of sub-Saharan Africa origin (50/59; 84.7%). At the time of sampling, median age was 42.4 years, ART uptake was almost universal (101/103; 98%) with a viral load less than 50 copies/ml in 93.2% of the patients, and 97.1% had CD4⁺ T cell count more than 350 cells/ml. The median duration between last TT booster and

Table 1. Characteristics of the individuals ($n=103$) included in the study at the time of tetanus vaccination and antitetanus antibody determination according to the region of origin.

	Time of vaccination			Time of sampling		
	Europe $N=44$	Outside Europe $N=59$	P	Europe $N=44$	Outside Europe $N=59$	P
Age (median)	42.3	42.6	0.6	49	50.5	0.8
Male n (%)	38 (86.4)	24 (40.7)	<0.01			
Female n (%)	6 (13.6)	35 (59.3)				
HIV-1 viral load <50 copies/ml n (%)	30/38 (78.9)	44/56 (78.6)	1	41/44 (93.2)	55/59 (93.2)	1
CD4 ⁺ T cell count – median (IQR)	646 (574–840)	521 (369–719)	<0.01	817 (663–1058)	699 (548–876)	0.02
CD4 ⁺ T cell count >350cells/ml n (%)	38/39 (97.4)	48/57 (84.2)	0.03	43 (97.7)	57 (96.6)	0.7
Nadir CD4 ⁺ T cell count <200 cells/ml n (%)	6/39 (15.4)	24/31 (43.6)	<0.01	7/44 (15.9)	25/59 (42.4)	<0.01
Antiretroviral therapy n (%)	36/44 (81.2)	48/59 (81.4)	1	43/44 (97.7)	58/59 (98.3)	0.8
Months since HIV infection diagnosis median (IQR)	108.1 (27–150.5)	105.5 (39.5–150)	0.9	166.5 (119.3–249.3)	174.8 (127.3–221.1)	0.9
Months since initiation of ART median (IQR)	38.5 (3.5–108)	60 (8–104)	0.6			

sampling was 5.6 years (IQR 2.6–8.9) and was similar between Europeans and non – Europeans [6 years (IQR 3–8.6) and 5.6 years (2.5–9.1), respectively]. At the time of tetanus toxoid immunization, non - European individuals had lower median CD4⁺ cell count (521 vs. 646 cells/ml, $P < 0.01$) and also higher proportion of individuals with nadir CD4⁺ T cell count less than 200 cells/ml (43.6% vs. 15.4%, $P < 0.01$). There was similar proportion of individuals with undetectable viral load and ART uptake between the two groups (Table 1).

Among all PWH recruited in the study, median antitetanus toxoid antibody (ATA) titers was 0.926 IU/ml (IQR: 0.467–1.626) and 6.8% (7/103) of the individuals had ATA titers less than 0.1 IU/ml.

Duration of tetanus toxoid immunity

Using a linear regression model, half-life of tetanus toxoid specific antibody was estimated at 9.9 years (95% CI: 5.5–50) in the whole cohort (Fig. 1a).

In order to assess the impact of region of origin on ATA decay rate, we used a linear regression model that included time from vaccination to ATA testing (b1), the variables European or not (b2), and the interaction between European and non-European groups and the time since vaccination (b3). Overall, both the model ($Pr > F < 0.0001$) and the interaction between the two groups was significant (b 0.07618; $Pr > t \frac{1}{4} 0.0012$), indicating a difference in the decay rate (i.e., slope) between European and non-European groups. On the basis of the data of individuals born outside Europe, halflife was estimated in non-European subjects: 4.4 years (95% CI: 2.9–8.5) (Fig. 1c). On the basis of the data from the European group, the coefficient of the decay rate is not significant (B $\frac{1}{4} 0.0073$; $P \frac{1}{4} 0.634$). Although large, the half-life could not be estimated (Fig. 1b).

Another linear regression model using the subgroups of patients with CD4⁺ cell count nadir less than 200 and more than 200 cells/ml was not conclusive regarding a difference in antibody decay rate: the model was significant ($Pr > F \frac{1}{4} 0.0032$), but the estimated coefficients were not, indicating that the slope were not different.

The model indicates that antibody titers will fall below the WHO threshold of protection (0.1 IU/ml) after 37 years in the whole cohort and after 17.9 years in non - European individuals.

Impact of baseline parameters with tetanus toxoid seropositivity

Median duration between vaccination and sampling was similar between individuals with baseline CD4⁺ T cell count less than 350 and more than 350 cells/ml (6.7 and 5.2 years, respectively). Individuals with baseline CD4⁺ T cell count less than 350 cells/ml had a higher risk of being seronegative at the time of sampling (OR $\frac{1}{4} 5.7$; 95% CI 1.2–27.9, $P \frac{1}{4} 0.049$) as compared to individuals with CD4⁺ T cell count more than 350 cells/ml. Individuals born outside Europe had more frequently a CD4⁺ T cell count less than 350 cells/ml as compared to individuals born in Europe (15.8% vs. 2.6%, $P \frac{1}{4} 0.03$). No impact of viral load and ART use at the time of immunization and TT seropositivity was found.

Discussion

In the study, we assessed the durability of tetanus toxoid specific seroprotection in a cohort of PWH using a linear regression model. We found a half-life of tetanus toxoid specific antibody of 9.9 years (95% CI: 5.5–50). Previous study using the same method but performed in a cohort of

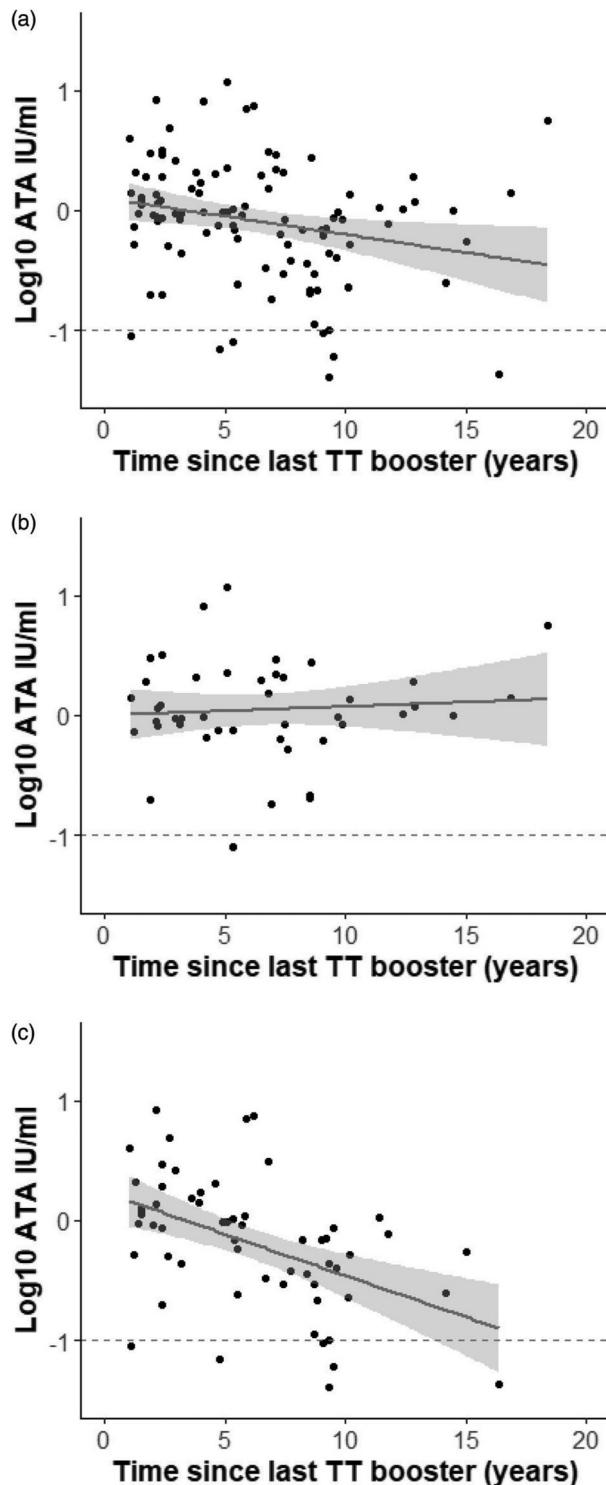


Fig. 1. Antitetanus toxoid antibody levels in people with HIV as a function of time since last vaccine booster in years in (a) the whole cohort ($n=103$); (b) PWH born in Europe ($n=44$); and (c) PWH born outside Europe ($n=59$). Solid red line represents the fitted regression line corresponding to the antibody half-life decay rate, and the shaded grey region represents the upper and lower bound of 95% confidence interval (CI) for the cross-sectional antibody half-life

HIV-negative individuals living in the USA found a half-life of 14 years (95% CI: 11–17) for tetanus toxoid specific antibodies.

A restricted analysis on the subgroup of individuals born outside Europe has shown a significantly reduced half-life of tetanus toxoid specific antibody [4.4 years (95% CI: 2.9–8.5)]. Two hypotheses could be generated to explain this finding. The first hypothesis could be related to the numbers of vaccine doses previously received before last tetanus toxoid booster. Most of the individuals born outside Europe originate from sub-Saharan Africa. Coverage of tetanus toxoid vaccine has been low in sub-Saharan Africa until recently [14,15]. The number of booster doses has been shown to impact the durability of tetanus toxoid seroprotection [5]. The lowest half-life observed in individuals born outside Europe could reflect lower uptake of tetanus toxoid vaccine in childhood adolescence and early adulthood, as previously reported. Indeed, different studies have found a high rate of seronegativity for different vaccine-preventable diseases in HIV-negative migrants as compared to native population [16]. Another study performed in France have found low vaccination coverage for tetanus toxoid, diphtheria, and polio among PWH born outside Europe, mainly originating from sub-Saharan Africa [17]. The environment has been shown to significantly impact immune response to vaccines in HIV-uninfected individuals by modulation of immune activation [18]. However, in our study, all individuals had documented vaccination in Belgium, after arrival, making an impact of the environment less possible.

The second hypothesis could be related to the immune status at the time of immunization but also before immunization. PWH born outside Europe had lower CD4⁺ T cell count at the time of immunization and also a higher proportion of subjects with a nadir CD4⁺ T cell count less than 200 cells/ml before immunization. Moreover, in the whole cohort patients with a CD4⁺ T cells count below 350 cells/ml at the time of immunization had a higher risk of tetanus toxoid seronegativity. These findings are in accordance with previous historical studies that reported a lower antibody response following tetanus immunization in individuals with low CD4⁺ cell count but also low nadir CD4⁺ cell count [8,9,19,20]. This suggests that not only lower CD4⁺ T cell count at the time of immunization but also lower nadir CD4⁺ cell count before immunization in PWH born outside Europe could impact the durability of ATA.

Considering the duration of tetanus toxoid seroprotection in the general population, WHO now recommends not to administer tetanus toxoid booster immunization in

estimation. The antibody decay rate (i.e., slope) was significantly different between PWH born in Europe and those born outside Europe ($P < 0.01$). Dashed red line represents correlate of protection of ATA according to WHO (0.1 IU/ml).

individuals who have completed the childhood immunization schedule [6]. Some countries have increased the interval timing of booster [7]. Whether PWH born in Europe and who have received required numbers of tetanus toxoid boosters could also benefit from booster dose with larger interval remains to be determined on a larger cohort. The British Guidelines for immunization of HIV- infected individuals recommend that patient with an uncertain vaccination history receive three vaccine doses at 1 month of interval follow by two reinforcing doses after 5 and 10 years. A booster dose for fully vaccinated PWH is recommended every 10 years [10].

This study has several limitations. First, we lack the information about the previous numbers of doses received by the individuals, notably those born outside Europe. Second, the cohort was mainly composed of PWH born outside of Europe and is not representative of the majority of PWH in care in Europe. Third, our model was not conclusive regarding a difference in antibody half - life decay rate between PWH with nadir CD4^b T cell count less than 200 and more than 200 cells/ml. We only provide indirect evidence of a possible impact of nadir and current CD4^b T cell count on the durability of ATA.

In conclusion, our results indicate that the half-life of tetanus toxoid antibody response in PWH individuals born outside Europe is lower as compared to previous reports in the general population [3,5]. PWH born outside Europe had lower CD4^b T cell count at the time of immunization and also higher proportion of nadir CD4^b T cell count less than 200 cells/ml. These findings indicate that the current WHO guidance not to administer booster doses of tetanus toxoid vaccine might not be adequate in PWH born outside Europe and/or with a low nadir CD4^b T cell count before immunization.

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Conflicts of interest

There are no conflicts of interest.

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